Scientists Uncover Molecular Clues About Origin of Cancer

Scientists at Johns Hopkins University in Baltimore, Maryland, have provided new insight into the inner workings of a member of a family of proteins, called human epidermal growth factor receptors (EGFRs), that are involved in abnormal tissue growth and cancer. This research, which was performed at the NSLS could lead to more efficient drugs aimed at preventing or treating some forms of cancer. The results were reported in the August 23, 2002 issue of *Science.*

"Little is known about the structures of the EGFR family members,"

Dan Leahy

says Dan Leahy, a biophysicist at the Howard Hughes Medical Institute (HHMI) and the lead author of the study, "yet they are involved in many human cancers, including breast, gastric, colon, and prostate cancers. Our study is a starting point to see how a possible drug might help prevent or cure these cancers."

Leahy and Hyun-Soo Cho, an HHMI postdoctoral student, studied a protein called human epidermal growth factor receptor 3 (HER3), which, like all the other EGFR proteins, is located on the surface of human cells. When HER3 binds to specific types of proteins, called ligands, its shape changes, and HER3 tells the cell to divide and multiply.

Though HER3 is not known to be involved in cancer, the abnormal production of its close relative, called HER2, is associated with particularly aggressive forms of breast cancer. But attempts to study the structure of HER2 have proven unsuccessful so far. Instead, by providing details of the molecular mechanisms of HER3, Leahy and Cho can now unveil some insight into the inner workings of HER2.

"It is usually very difficult to determine the structure of EGFRs," Leahy says. "It took us more than two years to get HER3's structure, and, now that we have it, it might be easier to understand how its relatives work."

HER3 consists of three parts, which are located outside the cell, in the cell membrane, and inside the cell. Leahy and Cho studied the outside part of HER3, called sHER3, which binds to specific ligands and changes its shape during the binding process.

To reveal sHER3's molecular details, the scientists used a method called x-ray diffraction. They first crystallized sHER3, and then bombarded the resulting crystal with x-rays produced by the NSLS. By looking at how the x-rays scattered off the crystal, Leahy and Cho determined the positions of the atoms inside sHER3, thus establishing its three-dimensional structure.

The structure showed that sHER3 is made of four regions, and suggested how ligands attach to sHER3 and induce shape changes. One unexpected aspect of the structure is what the scientists call the "snap" region – two finger-like loops that reach out toward one another and interact (**Figure 1**). Leahy and Cho also noticed that the size of the sHER3 binding site, which is comprised between regions I and III (**Figure 1**), is twice as big as the ligand size when the two finger-like loops interact.

"The 'snap' region seems to prevent a ligand from binding," Leahy says. "So, the two finger-like loops would have to detach from each other to allow a ligand to bind to sHER3, which informs the cell that it can grow and divide.

"If future studies confirm that this is how a ligand binds to sHER3, then it is pretty exciting," he adds. "This means that we can now think of new therapeutic approaches to modulating – preventing or stimulating –ligand-binding to HER3 and other members of the EGFR family."

Leahy and Cho suggest two approaches to developing such modulation. In the first approach, intended to prevent ligand-binding, the scientists propose to design mutant forms of ligands that would only bind to either region I or III, but prevent normal ligands to bind to HER3. As the finger-like loops remain attached to each other, the cell does not receive signals prompting it to grow and divide.

In the second approach, Leahy and Cho suggest to use molecules that would affect the binding between

the finger-like loops, by either breaking or reinforcing this binding, and thus favoring or inhibiting ligand-binding to HER3.

"I am very excited by the therapeutic opportunities that can be derived from the knowledge of the three-dimensional structure of this receptor," Leahy says. "This is just the beginning, but I am confident that similar studies will open more possibilities of tailoring appropriate drugs for the treatment of cancer."

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Hyun-Soo Cho and Daniel J. Leahy, "Structure of the Extracellular Region of HER3 Reveals an Interdomain Tether," *Science* **297**, 1330 (2002).

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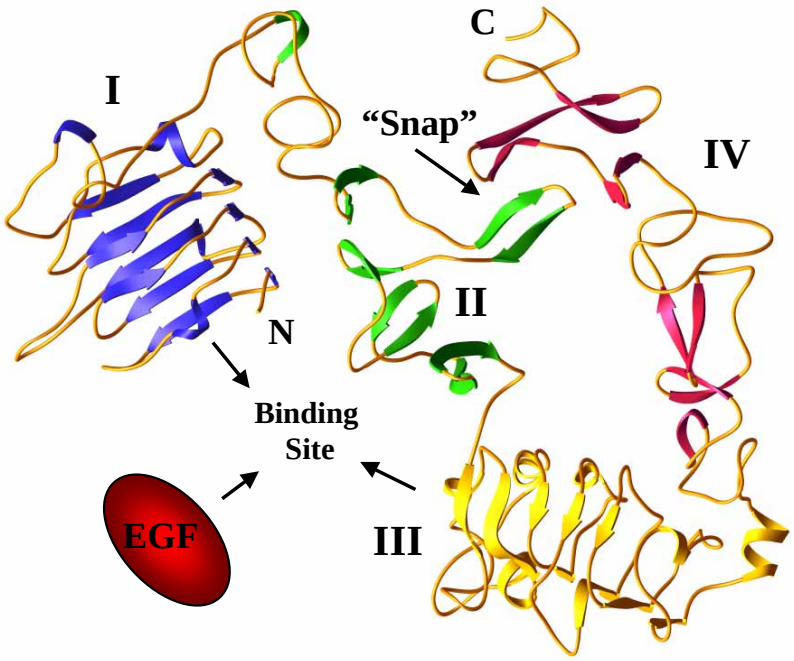

***Figure 1**. Ribbon diagram of the human epidermal growth factor 3 (HER3), showing domains I (blue), II (green), III (yellow), and IV (red). Disulfide bonds are shown in purple and gold. The results of Leahy and Cho's study indicate that a ligand (left) may bind to HER3 when the "snap" region opens, which bends domain II to the left and brings domains I and III close enough to "trap" the ligand between them.*